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U1S S2415

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(54) Abstract Title

Pharmaceutical formulation for the prevention of cardiovascular disease

(57) A formulation for the prevention of cardiovascular disease, in particular ischaemic heart disease and stroke, the use of said formulation and a method of preparing said formulation.

The said formulation is a combination of medicines contained in a single formulation for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population. The said formulation comprises active principals from at least two of the following four categories of drugs or agents:

i) a blood pressure lowering agent;
ii) a lipid-regulating agent;
iii) a platelet function altering agent; and/or
iv) a plasma/serum homocysteine lowering agent.

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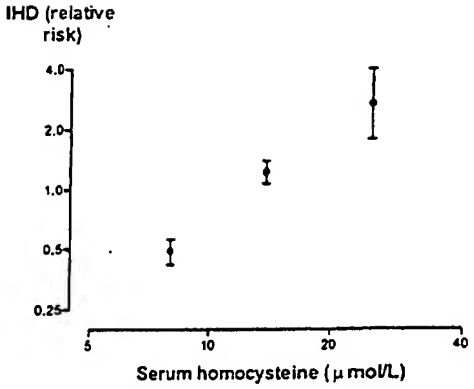
IHD (relative risk)
4.0
2.0
1.0
0.5
0.25
5
10
20
40
Serum homocysteine (μmol/L)

Fig. 4

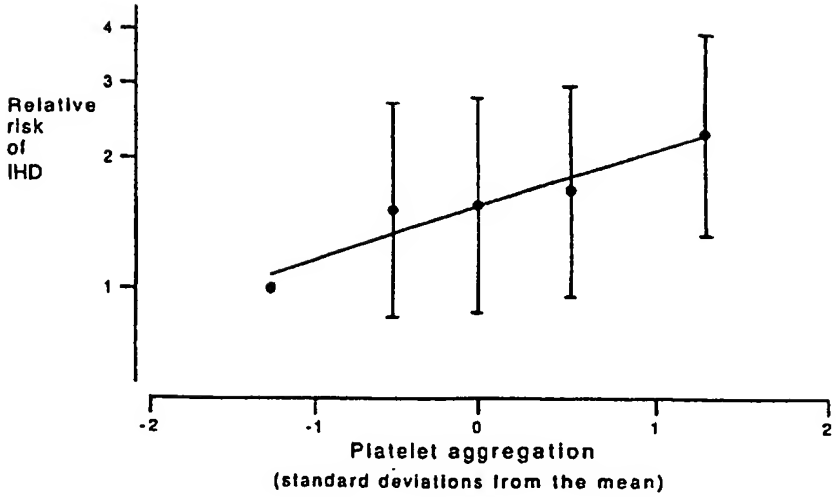
Relative risk of IHD
4
3
2
1
-2
-1
0
1
2
Platelet aggregation
(standard deviations from the mean)

Fig. 5

Formulation for the Prevention of Cardiovascular Disease

This invention relates to a formulation for the prevention of cardiovascular disease, in particular ischaemic heart disease and stroke, the use of said formulation and a method of preparing said formulation.

The formulation of the present invention is a combination of active principals contained in a single formulation for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population. The formulation of the present invention comprises active principals from at least two of the following four categories of drugs or agents:

i) a blood pressure lowering agent;

ii) a lipid-regulating agent;

iii) a platelet function altering agent; and/or

iv) a plasma/serum homocysteine lowering agent.

Ischaemic heart disease and stroke constitute the main causes of death in most economic developed countries, accounting for about a third of all adult deaths. Table 1 shows the numbers of deaths from heart disease and stroke in England and Wales in 1998, and also

Cause of death (ICD-9 code)	Men		Women	
	No of deaths	% of all deaths	No of deaths	% of all deaths
Ischaemic heart disease (410-4)	66009	25%	55024	19%
Stroke (430-8)	21432	8%	36046	13%
Heart failure (428), myocardial degeneration (429.1) and hypertensive disease (401-5)	5149	2%	9172	2%
Aortic aneurysm (441)	5829	2%	3668	1%
Total	98419	38%	103914	36%

Table 1 - Numbers of deaths from specified cardiovascular causes in men and women aged 15 and over, and the corresponding proportions of all deaths in men and women aged 15 and over, England and Wales 1998.

the smaller numbers of deaths from other cardiovascular causes that relate to the major cardiovascular risk factors. In total there are 200,000 deaths per year.

The main environmental causes of these diseases, apart from cigarette smoking, are conditions that increase blood pressure, increase serum cholesterol, increase plasma/serum homocysteine, or impair platelet function. The present policy for reducing the incidence of cardiovascular diseases in the general population is based on intervention only when the level of one of these risk factors (especially blood pressure) is found to be particularly high (approximately the top 5% of the distribution in middle aged people and the top 10% in elderly people). Drugs have tended to be used specifically for the control of high values of each risk factor: an individual found to have what is regarded as high blood pressure but an average serum cholesterol concentration will be given treatment to lower the blood pressure but not to lower the serum cholesterol. Drugs to alter platelet function (aspirin) and to lower homocysteine (folic acid) are rarely recommended for healthy persons. In persons who have had a non-fatal heart attack or stroke, treatment aimed at lowering blood pressure is given only if the blood pressure is at a level regarded as high (about top 10%), cholesterol lowering treatment is given if serum cholesterol is in roughly the upper half of the distribution, aspirin is routinely given, folic acid is generally not given.

The proposition underlying this invention is that this policy is inefficient. In seeking to identify persons who will have a heart attack or stroke, identifying only persons with especially high values of risk factors has a limited impact, because most cases of myocardial infarction and stroke occur in persons with risk factors close to the population average. Importantly, the average values of serum cholesterol, blood pressure and homocysteine in Western populations are high compared with the values in populations in which heart disease and stroke are rare. Also, treating persons in the top 5% or so of a distribution cannot make a significant impact on a group of diseases common enough to cause a third of all deaths. In offering treatment to reduce the risk of a heart attack or stroke, reducing each of these risk factors in isolation has a limited impact on the potential for reducing risk. Heart disease and stroke are common in Western countries, because the average values of all the important risk factors are high and their effects, being independent of each other, interact in a multiplicative or synergistic manner. A combined

treatment regimen aimed at changing several risk factors is necessary to achieve a substantial reduction in risk.

The formulation of the present invention comprises active principals from at least two of the following four different categories of drugs or agents:

i) a blood pressure lowering agent; preferably a diuretic, a beta-adrenoceptor antagonist (abbreviated beta blocker), an angiotensin-converting enzyme inhibitor (abbreviated ACE inhibitor), an angiotension-II receptor antagonist, a vasodilator antihypertensive drug, and/or a calcium-channel blocker; most preferably a diuretic, and/or a beta blocker and/or an ACE inhibitor;

ii) a lipid-regulating agent such as a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (abbreviated HMG CoA reductase inhibitor), also called a statin;

iii) a platelet function altering agent; preferably aspirin; and/or

iv) a plasma/serum homocysteine lowering agent; preferably folic acid.

The proposal to combine these four different categories of drugs into a single formulation is novel. No formulation is currently available that contains more than one category of these drugs in a single formulation. Currently available formulations combine two drugs that both lower blood pressure - thiazide diuretics and beta blockers, and thiazide diuretics and ACE inhibitors. No formulation is currently available that combines drugs that change different cardiovascular risk factors.

The physiological effects of these four different categories of drugs in reducing the risk of cardiovascular disease have been found to be independent of each other. The recognition of the combined effect of using these four different categories of drugs together is novel.

At the preferred dosages of these drugs the prevalence of the ratio of benefit to hazard, i.e. the ratio of the reduction in the incidence of cardiovascular disease to adverse effects of the drugs, is high. The estimation of the preventive effect of the formulation of the present invention and its application in a preventive setting is novel. In fact, a policy of treating a majority of the general population preventively against cardiovascular disease is contrary to the present policy for reducing the incidence of cardiovascular disease, which is based

on intervention only on one of the risk factors when the level of that risk factor is found to be particularly high.

Accordingly, the present invention provides a formulation comprising active principals from at least two of the following four categories:

i) at least one blood pressure lowering agent,

ii) at least one lipid-regulating agent,

iii) at least one platelet function altering agent, and/or

iv) at least one plasma/serum homocysteine lowering agent.

Preferably the formulation comprises active principals from two of the four categories; more preferably the formulation comprises active principals from three of the four categories; most preferably the formulation comprises active principals from all four categories. Optionally the formulation comprises more than one active principal from one or more of the four categories.

Preferably the blood pressure lowering agent is a diuretic, a beta blocker, an ACE inhibitor, an angiotension-II receptor antagonist, a vasodilator, and/or a calcium-channel blocker; more preferably the blood pressure lowering agent is a diuretic, and/or a beta blocker, and/or an ACE inhibitor.

Preferably the diuretic is a thiazide or thiazide-like diuretic. Preferably the thiazide thiazide-like diuretic is hydrochlorothiazide, chlorthalidone, indapamide, bendroflumethiazide, chlorothiazide, metolazone, cyclopenthiazide, polythiazide, mefruside, or xipamide. Most preferably the thiazide or thiazide-like diuretic is hydrochlorothiazide. Thiazide or thiazide-like diuretics are categorised in the British National Formulary Section 2.2.1 and other equivalent national formularies or pharmacopoeias. Preferably the hydrochlorothiazide is administered in an amount of from about 2.5 mg to about 62.5 mg per day; more preferably the hydrochlorothiazide is administered in an amount of from about 5 mg to about 37.5 mg per day; most preferably the hydrochlorothiazide is administered in an amount of about 12.5 mg per day.

Preferably the beta blocker is a β_1-selective adrenoceptor antagonist; preferably the β_1 selective adrenoceptor antagonist is atenolol, bisoprolol, betaxolol, metoprolol, celiprolol, or acebutolol. Alternatively the beta blocker is a non-selective beta-adrenoceptor antagonist; preferably the non-selective beta-adrenoceptor antagonist is pindolol, propranolol, oxprenolol, sotalol, timolol, or nadolol. Alternatively the beta blocker is a drug with combined β- and α-adrenoceptor blocking action; preferably this drug is carvedilol, or labetolol. Most preferably the beta blocker is atenolol. Beta blockers are categorised in the British National Formulary Section 2.4 and in other equivalent national formularies or pharmacopoeias. Preferably the atenolol is administered in an amount of from about 5 mg to about 125 mg per day; more preferably the atenolol is administered in an amount of from about 10 mg to about 75 mg per day; most preferably the atenolol is administered in an amount of about 25 mg per day.

Preferably the ACE inhibitor is enalapril, perindopril, captopril, cilazapril, trandolapril, fosinopril, quinapril, lisinopril, ramipril, or moexipril. Most preferably the ACE inhibitor is enalapril. ACE inhibitors are categorised in the British National Formulary Section 2.5.5.1 and in other equivalent national formularies or pharmacopoeias. Preferably the enalapril is administered in an amount of from about 1 mg to about 25 mg per day; more preferably the enalapril is administered in an amount of from about 1.5 mg to about 15 mg per day; most preferably the enalapril is administered in an amount of about 5 mg per day.

Preferably the angiotension-II receptor antagonist is losartan. Angiotension-II receptor antagonists are categorised in the British National Formulary Section 2.5.5.2 and in other equivalent national formularies or pharmacopoeias. Preferably the losartan is administered in an amount of from about 5 mg to about 125mg; more preferably the losartan is administered in an amount of from about 10 mg to about 75 mg per day; most preferably the losartan is administered in an amount of about 25 mg per day.

Preferably the vasodilator antihypertensive drug is hydralazine. Vasodilator antihypertensive drugs are categorised in the British National Formulary Section 2.5.1 and in other equivalent national formularies or pharmacopoeias. Preferably the hydralazine is administered in an amount of from about 2.5 mg to about 62.5 mg per day; more preferably

the hydralazine is administered in an amount of from about 5 mg to about 37.5 mg per day; most preferably the hydralazine is administered in an amount of about 12.5 mg per day.

Preferably the calcium-channel blocker is amlodipine. Calcium-channel blockers are categorised in the British National Formulary Section 2.6.2 and in other equivalent national formularies or pharmacopoeias. Preferably the amlodipine is administered in an amount of from about 0.5 mg to about 12.5 mg per day; more preferably the amlodipine is administered in an amount of from about 0.8 mg to about 7.5 mg per day; most preferably the amlodipine is administered in an amount of about 2.5 mg per day.

The most preferred doses named above are half of the doses at the lower end of the therapeutic range recommended in the British National Formulary. This is in order to maximise the therapeutic benefit of the combination of agents, while minimising the risks of adverse effects of the individual agents.

Preferably the formulation of the present invention comprises more than one blood pressure lowering agent. Preferably the formulation comprises one or more blood pressure lowering agents selected from a diuretic, a beta blocker, and/or an ACE inhibitor. More preferably the formulation comprises two blood pressure lowering agents selected from a diuretic, a beta blocker, and/or an ACE inhibitor. Most preferably the formulation comprises three blood pressure lowering agents selected from a diuretic, a beta blocker, and an ACE inhibitor.

Preferably the lipid-regulating agent is a serum cholesterol lowering agent. Preferably the serum cholesterol lowering agent is a statin. Preferably the statin is atorvastatin, simvastatin, cerivastatin, fluvastatin, or pravastatin. Most preferably the statin is atorvastatin. Lipid-regulating drugs are categorised in the British National Formulary Section 2.12 and in other equivalent national formularies or pharmacopoeias. Preferably the atorvastatin is administered in an amount of from about 2 mg to about 50 mg per day; more preferably the atorvastatin is administered in an amount of from about 3 mg to about 30 mg per day; most preferably the atorvastatin is administered in an amount of about 10 mg per day.

Preferably the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, or a glycoprotein IIb/IIIa receptor inhibitor such as abciximab, or a non-steroidal anti-inflammatory drug such as ibuprofen. Most preferably the platelet function altering agent is aspirin. Platelet function altering agents are categorised in the British National Formulary Section 2.9 and in other equivalent national formularies or pharmacopoeias. Non-steroidal anti-inflammatory drugs are categorised in the British National Formulary Section 10.1.1 and in other equivalent national formularies or pharmacopoeias. Preferably the aspirin is administered in an amount of from about 15 mg to about 500 mg per day; more preferably the aspirin is administered in an amount of from about 25 mg to about 250 mg per day; most preferably the aspirin is administered in an amount of about 75 mg per day.

Preferably the plasma/serum homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12. Most preferably the plasma/serum homocysteine lowering agent is folic acid. Preferably the folic acid is administered in an amount of from about 0.2 mg to about 4 mg per day; more preferably the folic acid is administered in an amount of from about 0.4 mg to about 2 mg per day; most preferably the folic acid is administered in an amount of about 0.8 mg per day.

Most preferably the formulation comprises:

i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,

ii) about 10 mg atorvastatin as lipid-regulating agent,

iii) about 75 mg aspirin as platelet function altering agent, and

iv) about 0.8 mg folic acid as plasma/serum homocysteine lowering agent.

All preferred dosages are calculated to be at levels optimising the ratio of benefit to hazard, i.e. the ratio of reduction of the risk of cardiovascular disease to the risk of adverse effects of the administered agent.

Optionally the formulation of the present invention further comprises an active principal from a fifth category comprising anti-oxidants. Preferably the antioxidant is vitamin E.

The formulation of the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal (including patches), airway (aerosol), rectal and topical (including buccal and sublingual) administration. Preferably the formulation of the present invention is provided in a form suitable for oral administration. For oral administration, the formulation of the present invention is preferably in the form of a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension.

Tablets for oral use may include the components mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the components are mixed with a solid diluent, and soft gelatin capsules wherein the components are mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

The desired dose is preferably presented once daily, but may be dosed as two, three, four or more sub-doses administered at appropriate intervals throughout the day. Preferably the active principals are present in the tablet, capsule, pill, powder, granules, a solution, or suspension in amounts suitable for administration once, twice, or three times per day. More preferably the active principals are present in the tablet, capsule, pill, powder, granules, a solution, or suspension in amounts suitable for administration once per day.

Preferably the formulation is used as a medicament. More preferably the formulation is used as a medicament for the prevention of cardiovascular disease. More preferably the formulation is used as a medicament for the prevention of ischaemic heart disease and stroke.

Preferably the formulation is used in men and women above a specified age for the reduction in the risk of cardiovascular disease. Alternatively the formulation is used in men and women with an estimated risk of cardiovascular disease above a specified level, wherein the risk is determined by measurement of risk factors used in conjunction with a person's age and sex. The formulation is also used in persons with a clinical history of coronary artery disease or cardiovascular disease irrespective of age or the values of risk factors.

Preferably the use of the formulation of the present invention reduces the risk of cardiovascular disease by at least 80%.

The present invention further provides the use of the formulation of the present invention for the manufacture of a medicament for the prevention of cardiovascular disease, preferably the manufacture of a medicament for the prevention of ischaemic heart disease or stroke. Preferably the medicament is used in men and women above a specified age for the reduction in the risk of cardiovascular disease. Preferably the medicament is used in men and women with an estimated risk of cardiovascular disease above a specified level, wherein the risk is determined by measurement of risk factors used in conjunction with a person's age and sex.

The present invention further provides a method of preparing the formulation of the present invention, comprising the steps of:

i) mixing the two or more active principals optionally with one or more pharmaceutically acceptable excipients, and

ii) forming the mixture into a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension suitable for oral administration to a patient.

Figure 1 is a graph showing the relative risk (95% confidence limits) of stroke according to blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 2 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease (IHD) according to blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 3 is a graph showing the mortality (95% confidence limits) from ischaemic heart disease according to serum cholesterol (reference 2). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 4 is a graph showing the incidence (95% confidence limits) of ischaemic heart disease according to plasma/serum homocysteine (reference 3). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 5 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease according to platelet aggregation (reference 4). The vertical axis is plotted on a logarithmic scale.

For each of the factors that affect the risk of heart disease and stroke and that can be favourably altered by drug therapy (blood pressure, serum cholesterol, plasma/serum homocysteine and platelet function), the relationships with heart disease and stroke are continuous across the range of values in Western populations. The higher the value of the risk factor, the greater is the risk of heart disease and stroke; an increased risk is not confined to persons with unusually high values of the risk factors. For each of the four risk factors, this continuous proportionate relationship has been established by two classes of evidence.

The first is a series of epidemiological studies in which measurements were made on a large number of persons and the values of the risk factors correlated against the subsequent incidence of heart attacks and stroke. Figures 1 to 5 show five sets of data on the relationships between cardiovascular risk factors and the incidence of ischaemic heart disease or stroke (namely, blood pressure and stroke, blood pressure and ischaemic heart disease, serum cholesterol and ischaemic heart disease, plasma/serum homocysteine and ischaemic heart disease, body mass index and ischaemic heart disease). The data are either from single large epidemiological studies or from studies in which the data from several

smaller studies have been combined (references 1-4). The study populations have been divided into subgroups (five equal subgroups in three of the five relationships shown) according to ranked values of the risk factor, as shown on the horizontal axes. Incidence, on the vertical axes, is plotted on a logarithmic (or proportional) scale. In each case the relationship is well described by a straight line, and in Figures 1 to 4 the 95% confidence intervals on each of the estimates of incidence are inconsistent with a relationship that is markedly non-linear. The linear relationship indicates that given a change in one of the risk factors from any point on the distribution is associated with a constant proportionate change in the risk of heart disease and stroke.

The second class of evidence is randomised controlled trials in which medication was given to lower the risk factors. Randomised trials have shown that drugs that lower blood pressure produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting blood pressure was high or average (reference 5). Similarly, randomised trials have shown that drugs that lower serum cholesterol have produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting concentration of serum cholesterol was high or average (references 6-7). Randomised trials have shown that aspirin reduces the incidence of heart attacks and stroke in both high risk and low risk persons (reference 8) (platelet function was not measured in the aspirin trials). For plasma/serum homocysteine no randomised trials are yet available, but evidence is available on persons with different genetic disorders that increase homocysteine concentration to varying extents; the increase in risk of cardiovascular disease in the different disorders is commensurate with the increase in homocysteine (references 3, 9).

Because of this continuous proportionate relationship between each of these risk factors and the incidence of ischaemic heart disease and stroke, it would be appropriate to alter all four of them in a person whose risk is high for any reason - a particularly high blood pressure for example, some genetic predisposition (recognised or unrecognised), or simply increasing age. The decision that preventive treatment in an individual is worthwhile should be based on the person's overall level of risk of a heart attack or stroke, not on the level of a particular risk factor. Because of the constant proportionate relationship, the benefit will be greater in those whose risk is greater. The preferred approach therefore is

to use all these agents to lower risk in persons whose existing overall risk is above a specified level. There is a need for a treatment strategy and a formulation that will combine the benefits of all of them, while minimising the occurrence of adverse effects (thereby increasing the potency: hazard ratio), and for the formulation to be available on a wide scale to individuals above a specified risk of having a major cardiovascular episode.

Despite the aetiological importance of the cardiovascular risk factors, their effectiveness in predicting risk in an individual is relatively weak (reference 10). A more important determinant of risk is age: the incidence of myocardial infarction and stroke doubles with every eight years of advancing age. By contrast, a doubling of risk occurs over a wide span of the distributions of the four risk factors (references 3, 4, 11, 12) (approximately from the 5th centile of the distributions to the 50th, or from the 50th to the 95th). Sex is also an important determinant of risk - the incidence in women at any age is about the same as that in men ten years younger. However, the single most important determinant of a person's risk is the presence of existing disease: in a person who has already had a heart attack or a stroke, for example, the risk of death from cardiovascular disease is about 5% per year, irrespective of age, sex, or the values of the risk factors.

The formulation of the present invention contains various components all designed to reduce the risk of cardiovascular disease by changing different predisposing risk factors. The formulation is prepared in doses that maximise efficacy and minimise adverse effects. Preferably the formulation is offered to all persons above a certain age or risk cut-off. The start of treatment could be determined firstly by a person's history of existing disease: any person with a history of previous myocardial infarction or angina, or a previous stroke or transient ischaemic attack, irrespective of age, sex, or the values of the risk factors, would be at sufficient risk to take the integrated formulation. In persons with no history of past disease, the start of treatment could be determined simply by a person's age and sex so that all men above a specified age (say 50 years) would take the integrated formulation each day and women could follow the same strategy but start at an older age (say at age 60 years). Alternatively, treatment could begin when a person's annual risk of ischaemic heart disease and stroke, calculated from their age, sex, and easily measurable risk factors (for example smoking, blood pressure and body mass index) was above a specified value. Such a policy would be substantially more effective than the current practice of using

pharmacological agents specific for a single risk factor and doing so only in individuals with high values of that risk factor or in individuals who have already suffered a major cardiovascular episode. The proposed new approach also takes into account, where current practice does not, that a history of previous cardiovascular disease and, in healthy persons, age are far more discriminatory measures of high risk than any of the cardiovascular risk factors.

Table 2 shows the risk factors altered by each of these drugs, the amount by which each one is changed on average by the preferred dosage, and the resulting expected reduction in the risks of ischaemic heart disease and stroke. Table 2 also shows that all the drugs in combination reduce the risk of ischaemic heart disease by an estimated 88% and of stroke by an estimated 86%. This combined estimate is based on the fact that the effects on the four different risk factors are unrelated and so the expected effects of changing each one will be independent of each other. This expectation is supported by two classes of evidence. First, epidemiological studies (in which the values of the risk factors were measured in many thousands of persons and the distribution of values examined in those who subsequently died of heart disease and stroke and those who did not) have shown that blood pressure, serum cholesterol, platelet function, and plasma/serum homocysteine are largely independent of each other in relation to the risk of cardiovascular disease (references 2, 3, 6, 218). For example the ratio of the risk of a disease event in persons with high blood pressure and the risk in persons with low blood pressure is similar, irrespective of the values of cholesterol and other risk factors. Second, some randomised clinical trials have used combinations of two of the drugs (for example beta blockers and aspirin) and have shown that the effects are independent (that is, the relative risk in patients who took two drugs (compared with the risk in those who took none) was similar to the relative risk in persons taking one of the drugs multiplied by the relative risk in persons taking the other drug). Accordingly, the effect of the different drugs in combination in Table 2 has been calculated by multiplying the effects of each as shown in footnotes h and j.

Drug	Example (daily dose)	Associated physiological variable (reduction produced by drug)	Expected reduction in risk of: ischaemic heart disease	stroke
Thiazide diuretic Beta blocker ACE inhibitor	Hydrochlorothiazide (12.5 mg) Atenolol (25 mg) Enalapril (5 mg)	Blood pressure (12 mmHg diastolic)[a]	43%[b]	63%[b]
Statin	Atorvastatin (10 mg)	Serum cholesterol (1.8 mmol/l)[c]	61%[d]	50%[d]
Aspirin	Aspirin (75 mg)	Platelet aggregation	38%[e]	15%[e]
Folic acid	Folic acid (0.8 mg)	Plasma/serum homocysteine (3 μmol/l)[f]	15%[g]	10%[g]
All drugs in combination			88%[h]	86%[j]

Table 2 - The constituent drugs in the proposed combined formulation, the cardiovascular risk factors that each alter, the amount by which each factor would be changed, and the resulting expected reduction in risk of ischaemic heart disease and stroke.

[a] Estimate obtained by us from an analysis of the blood pressure reduction according to dose in 187 randomised placebo controlled trials of thiazide or thiazide-like diuretics, beta-blockers and ACE inhibitors (references 13-199).

[b] Reduction in risk to be expected from the blood pressure reduction of 12 mmHg diastolic, from published analyses of cohort studies and randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1,5).

[c] From published randomised placebo controlled trials of atorvastatin (reference 200).

[d] The reduction in risk to be expected from the serum cholesterol reduction of 1.8 mmol/l, from published analyses of cohort studies and randomised controlled trials of serum cholesterol and ischaemic heart disease, and of randomised controlled trials of serum cholesterol reduction and stroke (references 6, 201, 202).

[e] Estimate obtained by us from an analysis of the results of 14 randomised controlled trials of aspirin in dosage of 50-100 mg daily and the incidence of ischaemic heart disease and stroke (references 203-216).

[f] A meta-analysis of published randomised controlled trials of folic acid in doses between 1 mg and 5 mg showed that the maximum reduction in plasma homocysteine is 3 μmol/l and that this maximum reduction is produced by a folic acid dose of 1 mg (reference 217); an unpublished randomised controlled trial performed by us has suggested that a folic acid dose of 0.8 mg is the lowest dose that produces this maximum reduction in homocysteine.

[g] The reduction in risk to be expected from the reduction in plasma homocysteine of 3 μmol/l from the results of cohort studies of homocysteine and cardiovascular disease (references 3, 9).

[h] 100% - [(100% - 43%) x (100% - 61%) x (100% - 38%) x (100% - 15%)] = 88%.

[j] 100% - [(100% - 63%) x (100% - 50%) x (100% - 15%) x (100% -10%)] = 86%.

Table 3 shows estimates of the prevalence of adverse effects from each of the medications when taken in the preferred dose. The dose of each medication has been chosen to maximise the ratio of benefit to hazard. It is recognised that some persons taking a combination of six drugs would develop adverse effects that were unacceptable. The adverse effects attributable to each of the component medications would be made clear to persons taking the combined formulation and alternative formulations omitting one or more of the component ingredients, with or without a substitute ingredient, would be available for persons unable to tolerate one component.

Drug	Example (daily dose)	Commonest adverse effects	Prevalence of any adverse effect in randomised trials (treated minus control)	Prevalence of serious adverse effects (those that warranted withdrawal from randomised trial)
Thiazide diuretic	Hydrochlorothiazide (12.5 mg)	dizziness, impotence, nausea	1.4%[a]	0.1%[a]
Beta blocker	Atenolol (25 mg)	cold extremities, fatigue, dizziness	5.6%[a]	0.9%[a]
ACE inhibitor	Enalapril (5 mg)	cough	2.1%[a]	0.2%[a]
Statin	Atorvastatin (10 mg)	-	0.1%	< 0.1%
Aspirin	Aspirin (75 mg)	bleeding, indigestion	1.8%[b]	0.7%[b] (mainly rectal or urinary bleeding)
Folic acid	Folic acid (0.8 mg)	-	< 0.1%	< 0.1%

Table 3 - The estimated prevalence of adverse effects of each of the six drugs to be included in the integrated formulation

[a] Estimate obtained by us from an analysis of the prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199).

[b] Estimate obtained by us from an analysis of the prevalence of adverse effects in 14 randomised placebo controlled trials of aspirin in dosage between 50 and 100 mg (references 203-216).

The doses of the first three drugs listed in Tables 2 and 3 (the drugs used to lower blood pressure) are half the present standard (or recommended) dose. Table 4 shows the reduction in blood pressure and in the incidence of ischaemic heart disease and stroke, and

the prevalence of adverse effects, from using half standard dose (as in Tables 2 and 3) and from using the present standard (or recommended) dose. There is little loss of efficacy using half standard dose, but the prevalence of adverse effects is reduced by almost half. In other words, the ratio of benefit to hazard is greater. The preferred dose of aspirin is the dose generally used in the prevention of cardiovascular disease (75 mg); this is much less than the dose necessary to relieve pain.

	Half standard dose (preferred dose)	**Standard dose**
Reduction in diastolic blood pressure	12 mmHg	15 mmHg
Proportionate reduction in incidence of:		
ischaemic heart disease	43%	50%
stroke	63%	71%
Prevalence of adverse effects	9%	16%

Table 4 - The combined effect of three drugs that lower blood pressure (a thiazide diuretic, a beta blocker and an ACE inhibitor) in lowering blood pressure, and reducing the incidence of ischaemic heart disease and stroke, together with the combined prevalence of adverse effects, according to whether the drugs are given in half standard dose or standard dose.

Estimates were obtained by us from an analysis of the blood pressure reduction and prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199). The corresponding reductions in incidence of ischaemic heart disease and stroke are those to be expected from the blood pressure reductions, from published analyses of cohort studies and randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1, 5).

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope of the invention, which is defined by the following claims only.

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Claims

1. A formulation comprising active principals from at least two of the following four categories:

i) at least one blood pressure lowering agent,

ii) at least one lipid-regulating agent,

iii) at least one platelet function altering agent, and/or

iv) at least one plasma/serum homocysteine lowering agent.

2. The formulation of claim 1, wherein blood pressure lowering agent is a diuretic, a beta blocker, an ACE inhibitor, an angiotension-II receptor antagonist, a vasodilator antihypertensive drug, and/or a calcium-channel blocker.

3. The formulation of claim 2, comprising one or more blood pressure lowering agents selected from a diuretic, a beta blocker, and/or an ACE inhibitor.

4. The formulation of any one of the preceding claims, wherein the lipid-regulating agent is a statin.

5. The formulation of one of the any preceding claims, wherein the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, a glycoprotein IIb/IIIa receptor inhibitor, or a non-steroidal anti-inflammatory drug.

6. The formulation of any one of the preceding claims, wherein the plasma/serum homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12.

7. The formulation of any one of the preceding claims, comprising:

i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,

ii) about 10 mg atorvastatin as a lipid-regulating agent,

iii) about 75 mg aspirin as a platelet function altering agent, and

iv) about 0.8 mg folic acid as a plasma/serum homocysteine lowering agent.

8. The formulation of any one of the preceding claims, further comprising an active principal from a fifth category comprising anti-oxidants.

9. The formulation of any one of the preceding claims, provided in a form suitable for oral administration to a patient.

10. The formulation of any one of the preceding claims, wherein use of the formulation reduces the risk of cardiovascular disease by at least 80%.

11. Use of a formulation as claimed in any one of claims 1 to 10 for the manufacture of a medicament for the prevention of cardiovascular disease.

12. A method of preparing the formulation as claimed in any one of claims 1 to 10, comprising the steps of:

i) mixing the two or more active principals optionally with one or more pharmaceutically acceptable excipients, and

ii) forming the mixture into a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension suitable for oral administration to a patient.